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In re Application of:
Westbrook

Serial No.: 07/784,222

Filed: 10/28/91

For: METHODS AND COMPOSITIONS FOR THE DETECTION OF CHROMOSOMAL ABERRATIONS

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§ Examiner: D. Rees
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§ Group Art Unit: 1807
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§ Atty. Dkt: ARCD-010/PAR
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CERTIFICATE OF MAILING
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April 24, 1997
Date

David L. Parker

AMENDMENT AND REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. § 1.116

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is in response to the Office Action mailed February 25, 1997. The examiner is requested to enter the following amendments under 37 C.F.R. § 1.116(a). No fees are believed due in connection with this paper but, should any fees be deemed necessary, the Commissioner is authorized to deduct said fees from Arnold, White & Durkee Deposit Acct. No. 01-2508/ARCD:010/PAR.

23. (Amended) A genetic probe **[designated as c-H-abl and]** capable of hybridizing to **[the 3' end of the ABL gene, comprising]** at least a part of the last exon of the ABL gene, as illustrated in FIG. 5 and FIGS. 2B and 2C.

31. (Amended) The composition of claim 14 wherein the fusion gene encodes either of two proteins **[designated as]** p190 and p210.

RESPONSE TO OFFICE ACTION

Status of the Claims

Claims 1-4, 11, 12, 15, 16, 22, 23 and 31 have been amended. Claims 1-33 are presently in the case and are presented for reconsideration. A copy of the pending claims is attached hereto as Exhibit A. The specific grounds for rejection and applicant's response thereto are set out in detail below.

The applicant would like to thank examiner Rees for her many helpful and constructive comments during the course of this prosecution. Her statement concerning what might constitute allowable subject matter was particularly helpful. Claims 1-4, 11, 12, 15, 16, 22, 23 and 31 have been amended in accordance with the examiner's suggestions to more clearly point out the subject matter of the invention. These amendments improve the clarity of the claims and are believed proper on this basis. The amendments further present the rejected claims in better form for consideration on appeal and may be properly admitted under 37 C.F.R. § 1.116(a).

Rejection of Claims 1-22, 29, 31-33 Under 35 U.S.C § 112, First Paragraph.

The examiner has rejected claims 1-22, 29, 31-33 under 35 U.S.C § 112, first paragraph as lacking an enabling disclosure. The examiner raises a number of distinct points in finding a lack of enablement. It is assumed that, if these enumerated concerns are obviated, the claims would then be allowable. If the examiner raises further issues, applicants submit that the examiner is obliged to issue a non-final action, having raised new grounds in support of the instant rejection. Each of the examiner's remaining concerns is addressed below.

The examiner states that "the specification, while being enabling for compositions comprising probes of defined sequence, does not reasonably provide enablement for probes recited by the function of hybridizing to ABL nucleic acid flanking sequence or BCR nucleic acid flanking sequence." (Office Action mailed 2/25/97, pages 2-3) The Office Action points out that "flanking sequences" could be interpreted as being limited to ABL and BCR nucleic acids, or could be interpreted to encompass sequences quite distant from ABL and BCR. (*Id.* at 4) The Action correctly observes, however, that the breakpoints for the BCR/ABL translocation, as well as the sequences of both ABL and BCR, were known in the art at the time the invention was made. (*Id.* at 5)

Applicant has amended claims 1 and 2 to more clearly point out what is meant by the term "flanking sequence". Amended claim 1 clarifies that the ABL nucleic acid flanking sequence begins at ABL exon II (second ABL exon) and extends approximately 200 kb beyond the last ABL exon, while the BCR flanking sequence begins at the first exon of the major

breakpoint cluster region of BCR and extends approximately 200 kb beyond BCR exon I (first BCR exon). The skilled practitioner of the art would realize that any pair of probes capable of hybridizing to these flanking sequences, with one member of the pair binding on one side of the translocation breakpoint and the other member of the pair binding on the other side of the breakpoint, would be within the scope of the present invention.

Support for the amended claim 1 is found in the specification at least on pages 10, 20, 22-24, 31-32 and Figure 2. As shown in Figure 2, the portion of the ABL gene flanking the breakpoint in the p210 or p190 fusion genes extends from exon II to slightly beyond the last ABL exon. Probes binding to this portion of the ABL gene, used in combination with one or more probes binding to the flanking portion of the BCR gene, would have the utility disclosed in the specification of detecting the recombinant fusion genes. The binding site for the c-H-abl probe disclosed in the instant application encompasses the last exon of the ABL gene. (Figure 2) The specification discloses probes of up to 200 kb. (page 10, lines 5-6) A 200 kb probe that bound to at least a portion of the last exon of ABL could extend for up to 200 kb past the last ABL exon in the direction away from the translocation site and still retain the disclosed utility of detecting the recombinant fusion genes.

Similarly, Figure 2 shows that the portion of the BCR gene flanking the breakpoint in the recombinant p210 fusion gene extends from the 5' region of the major breakpoint cluster region of BCR to slightly past BCR exon I (first BCR exon). The binding site for the PEM12 probe disclosed in the instant application encompasses the 5' region of the major breakpoint cluster region, while the binding site for the MSB-1 probe encompasses exon I of BCR. (Figure 2) It

was well known in the art at the time of the instant invention that the 5' region of the major breakpoint cluster region of BCR contains at least a first exon. (*E.g.*, Bartram *et al.*, *Blut* 55: 505-511, 1987.) With a probe size of 200 kb, a probe that bound to at least a portion of exon I of BCR could extend for up to 200 kb past exon I in the direction away from the translocation site and still retain the disclosed utility of detecting the recombinant fusion genes.

Dependent claim 2 has been amended to clarify the meaning of "flanking sequences" in an alternative way, in terms of a first probe having the property of being capable of hybridizing with at least part of an exon in the portion of the ABL gene flanked by and including ABL exon II and the last ABL exon, and a second probe capable of hybridizing with at least part of an exon in the portion of the BCR gene flanked by and including BCR exon I and the first exon of the major breakpoint cluster region. This is more restrictive than independent claim 1, which includes potential binding sites from exon or intron sequences of ABL and BCR, as well as untranscribed portions of these genes. Applicant notes that a probe could bind to the last ABL exon or the first BCR exon and still extend for up to approximately 200 kb beyond these exons.

Support for the amendment to claim 2 is also found in the specification at least on pages 10, 20, 22-24, 31-32 and Figure 2. As shown on Figure 2B, all exons encompassed within the "flanking sequences" of claim 2 would have the property of flanking the translocation site for the p210 fusion gene. Pairs of probes capable of binding to at least a portion of an exon located on either side of the translocation site would have the utility disclosed in the specification of detecting the fusion gene. The specification discloses probes capable of binding to the first exon of BCR (MSB-1), the 5' region of the major breakpoint cluster region (PEM12) and the last exon

of ABL (c-H-abl). Applicant reiterates that it was well known in the art at the time of the instant invention that the 5' region of the major breakpoint cluster region of BCR contains at least a first exon. (*E.g.*, Bartram *et al.*, *Blut* 55: 505-511, 1987.)

Amended claim 4 recites probes hybridizing to sequences located within approximately 800 kb of each other. As suggested by the examiner, the earlier version of this claim read on sequences that could be much greater than 800 kb apart, thereby encompassing many more nonworking embodiments than working embodiments. The amended claim is supported by page 10, lines 20-21 of the specification, which states that "labelled flanking regions have to be approximately within 800 kb." Applicant submits that the claim, as amended, encompasses more working embodiments than nonworking embodiments and is properly allowable.

Amended claim 11 recites a first probe having the property of being capable of hybridizing to at least a portion of the last exon of the ABL gene and a second probe capable of hybridizing to at least a portion of exon I of the BCR gene. Such probes would have the utility disclosed in the specification of detecting both the p190 and p210 fusion genes. The amendment is supported at least by pages 10, 20, 22-24, 31-32 and Figure 2 of the specification. The MSB-1 and c-H-ras probes disclosed in the specification have the properties of hybridizing to at least portions of exon I of BCR and the last exon of ABL, as recited in claim 11. The skilled artisan reading claim 11 in light of the specification would realize that probes of up to 200 kb in size could bind to exon I of BCR or the last ABL exon and extend for some distance on either side of these exons.

The Action states that the specification is enabling for compositions comprising probes of defined sequence. (Office Action mailed Feb. 25, 1997, page 2) Applicant submits that the defining features of the probes are clearly recited in claims 1-33. Applicant further submits that, given the known sequences of ABL and BCR and the enabling nature of the specification for probes of defined sequence, any skilled practitioner of the art could have determined, without undue experimentation, additional probes within the ABL and BCR sequences having the same disclosed utility of binding on either side of the translocation site, thereby allowing detection of the recombinant p190 or p210 fusion genes.

Applicant submits that the claims as amended provide a clear and concise written description of the invention. Applicant further submits that it was well within the ability of the skilled artisan to make and use the invention, given the state of the art at the time of the invention, the information provided within the specification and the clarity of the amended claims. Applicant therefore requests reconsideration of the claims and withdrawal of the rejection.

Rejection of Claims 1-33 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-33 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant wishes to thank the examiner for her many helpful suggestions in this section of the Office Action. The examiner's specific objections are addressed below.

Applicant notes the claim 1 has been amended to clarify what "an ABL nucleic acid flanking sequence" and a "BCR nucleic acid flanking sequence" are. Claim 2 provides an alternative form of clarification for these terms. The nature of these clarifications has been described in the section above.

Claim 12 has been amended to omit the word "No."

The word "designated" has been removed from amended claims 15, 16 and 31. With regard to deposit of the probes under the terms of the Budapest Treaty, applicant assures the Patent Office that an acceptable deposit will be made on or before the date of payment of the issue fee in accordance with 37 C.F.R. § 1.809.

Claim 23 has been amended to remove the words "3' end of the ABL gene". The amended claim 23 recites a probe capable of hybridizing to at least a part of the last exon of the ABL gene. Applicant submits that the last exon of the ABL gene is clearly described in the specification and was well known in the art at the time of the instant invention.

As stated above, the word "designated" has been removed from amended claims 15, 16 and 31.

Applicant submits that it is fundamental patent law that claims are to be read in light of the specifications and both are to be read with a view to ascertaining the invention. *United States*

v. Adams, 383 U.S. 39, 15 L. Ed.2d 572, 86 S. Ct. 708 (1966). The standard for § 112, second paragraph is whether one skilled in the art would be able to determine what subject matter is claimed. *Hybritech, Inc. vs. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986).

Applicant submits that reading the specification and claims together, the skilled artisan would be able to determine the subject matter of claims 1-33, as amended. The meaning of the terms "ABL nucleic acid flanking sequence" and "BCR nucleic acid flanking sequence" have been clearly stated in the amended claims 1 and 2.

Figure 2 identifies those portions of the BCR and ABL genes included within the metes and bounds of the claimed invention. As noted by examiner Rees, the location of the ABL:BCR translocation breakpoints, as well as the sequences of BCR and ABL, were known in the art at the time the invention was made. (Office Action mailed Feb. 25, 1997, page 5)

Both claims 1 and 2 clearly recite those portions of the Philadelphia chromosome within the scope of the instant invention. In amended claim 1, the scope extends from the first exon of the major breakpoint cluster to approximately 200 kb past BCR exon I on one side of the translocation breakpoint, and from ABL exon II to 200 kb past the last ABL exon on the other side of the breakpoint. Given the known sequences of BCR and ABL and the known location of the translocation breakpoints, the skilled artisan would have been well able to determine the metes and bounds of the invention. This is even more clearly stated in claim 2, as the sequences of all exons within the recited nucleic acid flanking sequences were known in the art at the time of the invention.

Applicant submits that the claims as amended particularly point out and distinctly claim the subject matter of the invention. Applicant submits that the amended claims 1 and 2 and all dependent claims particularly point out and distinctly claim the regions flanking the BCR:ABL translocation sites within the subject matter of the invention. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 1, 4, 8, 9, 11, 12, 14, 17-20, 22, 23, 30, 31 Under 35 U.S.C. § 102

The Action has rejected claims 1, 4, 8, 9, 11, 12, 14, 17-20, 22, 23, 30 and 31 under 35 U.S.C. § 102(a) as being anticipated by Stephenson et al. (1987). Stephenson et al. teach synthetic oligonucleotides useful in the diagnosis of CML, teaching probes complementary to the bcr-abl splice site.

Applicant submits that the reference by Stephenson et al. does not anticipate the claims of the instant invention. Rejection under 35 U.S.C. § 102 is improper unless each and every element of the claimed invention is present in a single prior art reference. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986). Applicant submits that the instant invention incorporates an element that is missing from the reference by Stephenson et al. cited by the examiner.

It is an element of the instant invention that the probes of the claimed composition must be utilized in pairs. Independent claim 1 recites "a pair of probes, said pair comprising a first and second nucleic acid probe", in which the first probe binds to an ABL flanking sequence and the second probe binds to a BCR flanking sequence. The claim thus recites a pair of probes, one binding on either side of the translocation breakpoint. This element is incorporated into dependent claims 2, 4, 8, 9, 11, 12, 14, 17-20, 30 and 31.

Nowhere does Stephenson et al. teach the utilization of probes in pairs. Nowhere do Stephenson et al. even suggest the use of their probes in pairs, nor would they have had any motivation to use their probes in pairs. In contrast, the instant invention could only work with paired probes. Without a first and a second probe, one binding on either side of the translocation breakpoint, there would be no way to detect CML or ALL in accordance with the present invention.

At best, Stephenson et al. teach a multiplicity of probes, binding in the region around the bcr:abl translocation breakpoint. Although a multiplicity of probes admittedly encompasses a pair of probes, the requirement of using probes in pairs forms an additional element of the present invention, not taught by Stephenson et al.

Independently of the above-mentioned element, several of the amended claims are outside the scope of Stephenson et al. Amended claim 11 specifies a first probe capable of binding to at least a portion of the last exon of ABL and and second probe capable of binding to at least a portion of BCR exon I. The Office Action states on page 7 that Stephenson et al. teach

synthetic oligonucleotides complementary to a sequence in bcr exon 2 and a sequence in abl exon 2. Thus, both exon I of BCR and the last exon of ABL would be outside the teachings of this reference.

In claim 22, the word "region" has been deleted. The claim now recites a genetic probe capable of hybridizing to the first exon of the BCR gene. For the reasons cited above, this is outside the teachings of Stephenson et al.

Similarly, claim 23 has been amended to delete the phrase "the 3' end of the ABL gene". The claim now recites a probe capable of hybridizing to at least a part of the last exon of the ABL gene. Again, this is beyond the teachings of Stephenson et al.

For these reasons, applicant submits that the instant invention does not "read on" Stephenson et al. and rejection of the claims under 35 U.S.C. § 102 is improper. Reconsideration of the claims is respectfully requested.

Rejection of Claims 2 and 29 Under 35 U.S.C. § 103

The Action has rejected claims 2 and 29 under 35 U.S.C. § 103 as being unpatentable over Stephenson et al. (1987). The Action states that "Stephenson et al. meets all of the limitations of the claims except for the teaching of a labelled probe or the teaching that the probes are provided in a kit." (Office Action mailed 2/25/97 at page 8)

Applicant first notes that claim2 has been amended so that it no longer recites a labelled probe. Applicant submits that the amended claim 2 may no longer be properly rejected under 35 U.S.C. § 103 over Stephenson et al. Applicant further notes that claim 30 incorporates the limitations of amended claims 22 and 23. These claims now recite probes capable of hybridizing to the first exon of the BCR gene and at least a part of the last exon of the ABL gene. Therefore, the probes taught by Stephenson et al. no longer meet all the limitations of claim 30 besides the kit format, as the probes of Stephenson et al. were not capable of binding to either the first exon of BCR or last exon of ABL. (Office Action mailed 2/25/97 at page 7, last paragraph) Therefore, rejection of claims 2 and 30 under 35 U.S.C. § 103 is no longer proper and applicants request that the rejection be withdrawn.

It is significant that the MSB-1 probe of the instant invention binds to exon I of the BCR gene, while the c-H-abl probe binds to the last ABL exon. Thus, they are capable of detecting all BCR-ABL fusions that could predispose to CML or ALL. There is no equivalency between the probes taught by Stephenson et al. and the MSB-1 and c-H-ras probes taught in the instant invention. According to the Action, the probes of Stephenson et al. are complementary to bcr exon 2 and able exon 2. Thus, they are not capable of hybridizing with BCR exon I or the last ABL exon. The teaching of Stephenson et al. could not have made either the MSB-1 or c-H-ras probes or methods utilizing these probes obvious, since Stephenson et al. did not teach how to make or use these probes, nor did they teach any method for obtaining these probes. Stephenson et al. do not even suggest that it would be desirable to obtain probes such as MSB-1 or c-H-ras.

There is no teaching in Stephenson *et al.* that would provide a skilled practitioner of the art with either the guidance or motivation to make and use the instant invention. There is no suggestion in this references as to how a practitioner would obtain the MSB-1 or c-H-ras probes or their equivalents. Therefore, this reference cannot have provided a practitioner with the motivation to develop the instant invention. In the absence of such motivation, the cited reference only provides a mere "invitation to experiment" that cannot support an obviousness rejection. *In re O'Farrell*, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988).

Applicant respectfully traverses the assertion that "the art provides the motivation to provide compositions of the recited probes for the purposes of Southern analysis of chromosomal aberrations...." (Office Action mailed 2/25/97, page 10) Applicant reiterates that a feature of the instant invention is the use of probes in pairs. Applicant submits that the art at the time of the instant invention provided no motivation for the use of paired probes, particularly where each member of the pair was differentially labeled. At the time of the instant invention, the art generally taught two means of using probes for Southern analysis. The primer extension method provided a labeled single oligonucleotide for hybridization with target nucleic acids, while the nick translation method provided a multiplicity of labeled oligonucleotides. Neither of these techniques would have resulted in a pair of labeled probes. Applicant further submits that for the purpose of Southern blotting, there is no reason and no motivation to use paired probes.

For the reasons stated above, applicant respectfully submits that the examiner has failed to establish a *prima facie* case for obviousness. Applicant requests that the rejected claims be reconsidered in light of this argument.

Summary and Conclusion

In light of the foregoing comments, applicant submits that all pending claims are in condition for allowance and solicits an early indication to that effect. Should Examiner Rees feel that further discussion of any of the issues is merited, she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

David L. Parker
Reg. No. 32,165

ARNOLD, WHITE & DURKEE
P.O. Box 4433
Houston, TX 77210
(512) 418-3000

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